Visual Evoked MEG Fields in Migraine Patients

Susan M. Bowyer[1,2], Vijaya Nagesh[1], John E. Moran[1], Norman Tepley [1,2], and K.M.A. Welch[3]

[1]Henry Ford Hospital, Detroit, Michigan USA; [2]Oakland University, Rochester, Michigan USA
[3]University of Kansas School of Medicine, Kansas City, Kansas USA

Abstract
Visual evoked cortical magnetic fields (VECMF) were recorded during continuous visual stimulation in patients with migraine with aura (M+A) [1], migraine without aura (M-A), and normal subjects. Complex VECMFs were observed in M+A and in M-A but not in controls. Analysis, using Multi Resolution FOCUSS (MR-FOCUSS) [2,3] showed large extended primary visual cortical activation in M+A patients. M-A patients had more cortical activation than controls but less than the M+A patients. In normal subjects, activation was only observed in the primary visual cortex. VECMFs of varied amplitude, latency and waveform, were observed in widespread areas of the occipital cortex in M+A patients in contrast to consistent and physiological focal striate cortex evoked responses in normal subjects. These findings suggest that neuronal hyperexcitability underlies the potential for triggering abnormal neuroelectric events such as spreading depression throughout extensive regions of the occipital cortex of M+A patients.

1 Introduction

Visual evoked potentials (VEPs) from migraine subjects have been investigated by several researchers to evaluate their diagnostic value [4-7]. The studies utilized pattern reversal stimulus at various rates from 0.5 Hz to 24 Hz. Results as to whether or not VEPs can accurately diagnose migraine were inconclusive. In a previously published functional MRI-BOLD study, visual stimulation at 8Hz initiated spreading suppression of neuronal activation in M+A patients at rates compatible with experimental spreading cortical depression (SCD) [8]. We replicated this study utilizing MEG [1] and found further evidence to support an SCD-like event occurring during migraine aura.

This study investigated the visual evoked cortical magnetic field (VECMF) responses during visually-induced migraine aura, to ascertain whether these signals can further establish an association or distinguish between M+A and M-A. Based on the data obtained, VECMF results further support the theory of a hyperexcitable occipital cortex in both M+A and M-A patients.

2 Methods

2.1 Patient studies

Neuromagnetic fields (148-channel Neuromagnetometer, 4D Neuroimaging WH2500) were measured during visual stimulation of the occipital cortex in six M+A patients who had a history of migraines attacks triggered by visual stimuli (e.g. bright light, flashing lights, strobe lights), six M-A patients, and six normal control subjects with no history of migraine headache. Migraine patients were classified based on the International Headache Society (IHS) criteria [9]. No patients were taking preventive medications and none had suffered a migraine attack within the seven-day period preceding the study.

The stimulus consisted of a circular checkerboard pattern, with 50-degree radius and 5 degree check size that alternated black and white at 8 Hz. The pattern was projected onto an opaque white projection screen and delivered to the subject using a system of mirrors. Each subject was asked to focus on a black dot in the center of the oscillating image on the screen. All data were digitized at 290.64 samples per second, with a band pass of 0-50 Hz.

2.2 Data Processing

Data were filtered at 1-30 Hz and separated into three (3) averaged epochs, each containing ~500 pattern reversals. The first epoch was created from the first three (3) minutes; the second from minutes eight through ten (8-10) and the third from the minutes sixteen through eighteen (16-18) of data. To correlate MEG areas of cortical activity with specific anatomical structures, a standard MRI scan was manually rescaled to each subject's digitized head shape [10]. The MRI scan comprised of T1 sagittal images, 124 slices, and 256x256 matrix that included the entire skin surface of the head.

2.3 Data Analysis

2DII [2] is a current density source imaging technique that produces whole brain images of both focal and extended source structures that may be simultaneously active. The 2DII technique utilized approximately 3,000 cortical source locations derived from the MRI to model the continuum of cortical gray matter. Utilizing an iterative algorithm the 2DII technique transformed random initial amplitudes of the 3000-point cortical structure into a source structure corresponding to the magnetic field data. To ensure a robust result 20 solutions were used to create the images. MR-FOCUSS [3] utilizes the 2DII source structure and a least squares solution, which replaces the minimum norm technique in the FOCUSS [11] iterative algorithm. The localization results are displayed on the volumetric MRI scan.

2.4 Statistical Analysis

Mixed Models with Repeated Measures were used to analyze the Amplitude and Latency measurements of the treated groups over time. Fisher's exact tests were used to test for differences in VECMF MEG signal peak responses between group groups.

3 Results

All induced migraine with aura (M+A) patients experienced visual auras similar to their spontaneous auras. The six visually-induced M-A patients did not experience any adverse effects or visual symptoms. None of the six visually stimulated normal controls experienced aura.

Typical VECMF response MEG recordings are shown in figures 1-3. VECMF MEG signal peaks were observed in all M-A patients and controls but not in all M+A patients. Initial VECMFs responses were seen at 34 $\pm$ 6 ms for all control subjects and at 46 $\pm$ 12 ms for all M-A patients and 46 $\pm$ 12 for all M+A patients. A group effect was detected in testing the latency measurements: the M-A group mean was observed to be significantly larger than the Control group mean. No other group comparison tested significant in these latency measurement tests. (M+A vs control: p=0.1131 ; M-A vs M+A: p=0.3073, and M-A vs. control: p=0.0038).

Amplitudes of the peak to peak MEG wave from was 118 $\pm$ 48 fT for all control subjects and at 126 $\pm$ 44 fT for all M-A patients and 127 $\pm$ 62 fT for all M+A patients. There were no statistically significant differences detected between the groups within the amplitude measurements.

The peak amplitude was used to calculate the underlying source amplitude. The MR-FOCUSS technique was applied to localize areas of cortical activity arising from this response. Migraine patients had widespread neuronal activation unlike control subjects who had only focal primary visual cortex activation.

Figure 1 displays the VECMF response in a M+A patient. Peak latencies varied between epochs and were different for each subject. Amplitudes of these peak latencies also varied across the three epochs. The localization of cortical activity on the MRI scan depicted multiple regions of cortical activation, which were seen in the primary visual cortex as well as in the left occipito-parietal cortex. Most activation occurred in the right occipito-parietal/temporal region. Localization of the VECMF during the first 2 minutes was inconsistent across all M+A patients. Localization of the VECMF during the last 2 minutes was again inconsistent across all M+A patients. MEG waveforms seen in the figures include all channels in the occipital area overlaid with the peak latency of interest selected.

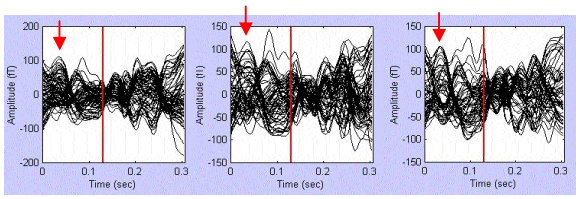

Figure 1. Visual evoked MEG data from a **migraine with aura** patient. A) MEG waveforms of the VECMF during the first epoch.; B) the second epoch, and C.) the last epoch. VECMF responses are inconsistent across the three epochs. Arrow denotes peak in the initial 50 ms

Figure 2 displays the VECMF responses in a typical control subject. The latencies of the VECMF throughout 20 minutes of visual stimulus were consistent across control (non-migraine) subjects. Amplitudes at peak latencies were similar across the three epochs. Localization of the VECMF during the first 2 minutes occurred at latency ~35 ms. Localization of Epoch 2 displayed reduced area of cortical activation in the MR-FOCUSS images. Localization of the VECMF during the last 2 minutes was consistent with the initial epoch and across control subjects. Peaks were localized to a small focal area of the striate cortex.

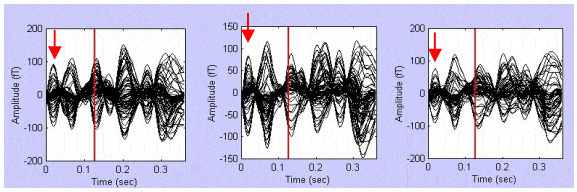

Figure 2. Visual evoked MEG data from **control (non-migraine) subject**. A) MEG waveforms of the VECMF during the first epoch at latency 35 ms, B.) epoch two 39 ms, and C.) the last epoch 35 ms. VECMF responses are consistent across the three epochs; see arrows.

Figure 3 displays the VECMF in a M-A patient. Peak latencies at 70 ms and 130ms were consistent across all three epochs. Peaks were imaged in extended areas of the striate cortex. Amplitude at peak latencies were similar across the three epochs. VECMFs from M-A were similar to controls in that there was a consistent response but the latency varied. Neuronal activation was similar to that seen in the M+A patient. Significant areas of neuronal activation were seen in the primary visual cortex, and the right occipital cortex during visual stimulation.

4 Discussion

To date, most studies of the visual evoked response studies have been inconsistent [4-7]. This investigation of VECMF utilizing MEG and a high frequency stimulation, provided more information about the hyperexcitability of both M+A and M-A patients. VECMFs reveal

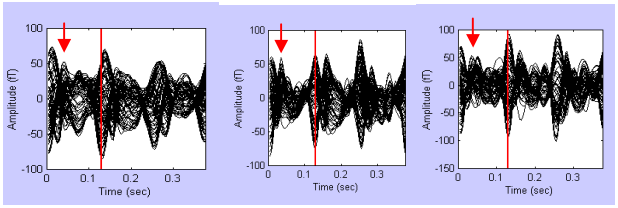

Figure 3. Visual evoked MEG data from a **migraine without aura** patient. A) MEG waveforms of the VEF during the first epoch latency 51ms ; B.) the second epoch 75 ms; and C.) the last epoch 47 ms. VECMF responses are consistent across the three epochs. Arrow denotes peak in the initial 50 ms. Significant areas of neuronal activation were seen in the primary visual cortex, and the right occipital cortex during visual stimulation.

extended cortical activation in primary visual cortex in M+A patients and M-A patients not seen in visually stimulated controls.

MEG measurements provide a direct measurement of neuronal excitation. We demonstrated that M-A patients appear to be on a continuum between M+A patients and control subjects. Visually evoked cortical activation, of inconsistent amplitude, latency and waveform, was observed in widespread areas of the occipital cortex in M+A patients, in contrast to consistent focal physiological evoked responses in striate cortex in normal subjects. M-A patients had wide spread cortical activation in the primary visual cortex and associated cortex. Though the latencies differences between M+A vs controls was not found to be statistically significant, this was due to a sample size of 3 out of 6 M+A peaks compared to 6 of 6 clear peaks. We hypothesize that this effect may be overcome with increased sample size.

Waves of neuronal excitation in a convoluted cortex generate complex MEG field patterns due to propagation in different directions across multiple sulci. MR-FOCUSS analysis of continuous MEG data [1] displays extended occipital cortical activation in M+A patients not seen in VECMFs of the same subject. These findings suggest that neuronal hyperexcitability underlies the potential for triggering abnormal neuroelectric events such as SCD throughout extensive regions of the occipital cortex of M+A patients.

Our recordings confirmed the hyperexcitability of widespread regions throughout occipital cortex in M+A and M-A providing the susceptibility for triggering SCD and aura in migraine sufferers [12]. Repetitive and frequent depolarization/repolarization of hyperexcitable cortical neurons may cause potassium accumulation in the extracellular space, sufficient to initiate SCD in regions of the brain. Since some M-A patients report that their migraines are triggered by noxious smells or specific foods, SCD may not be as easy to detect as in M+A, since SCD-like events may be triggered in deeper brain structures in M-A patients.

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